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(71) Applicant: BAKER NORTON PHARMACEUTICALS, INC. [US/US]; 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(72) Inventors: BLONDINO, Frank, E.; 6237 Rose Terrace, Plantation, FL 33317 (US). BRUCATO, Michael; 9801 N.W. 1st Avenue, Miami Shores, FL 33150 (US). BUENAFE, Maria, W.; 110 Southshore Drive #3–C, Miami Beach, FL 33141 (US).

(74) Agents: LEVI–MINZI, Simona, A. et al.; Baker Norton Pharmaceuticals, Inc., 4400 Biscayne Boulevard, Miami, FL 33137 (US).

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(54) Title: PRESSURIZED METERED DOSE INHALERS AND PHARMACEUTICAL AEROSOL FORMULATIONS

(57) Abstract

Provided are pressurized metered dose inhalers containing stable formulations of a β–agonist drug in suspension or solution. Also provided are aerosol formulations suitable for inhalation therapy containing a β–agonist drug in suspension or solution.

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PRESSURIZED METERED DOSE INHALERS AND PHARMACEUTICAL AEROSOL FORMULATIONS

1. Field of the Invention.

The invention relates to pressurized metered dose inhalers and aerosol formulations for inhalation therapy.

2. Background of the Invention.

Because of environmental considerations, chlorohydrocarbon and chlorofluorocarbon propellants for aerosol formulations for medical uses have been largely replaced by hydrofluoroalkanes such as 1,1,1,2-tetrafluoroethane ("HFA-134a") and 1,1,1,2,3,3,3,-heptafluoropropane ("HFA-227ea") that have been identified as safe for use in pressurized metered dose inhalers.

Such medicinal aerosol formulations are generally of the solution or suspension type. Each type is composed of, at least, the medicament and the propellant. Some formulations also include one or more special purpose adjuvants such as a cosolvent or a surfactant (EP O 372777). Conventional aerosol solution formulations contain low concentrations of a cosolvent more polar than the propellant. Conventional aerosol suspension formulations contain a surfactant rather than a cosolvent on a theory that the surfactant would prevent agglomeration of the particles, their adhesion to the walls of the aerosol container, and provide for lubrication of the dispensing valve ("actuator"). (US 3,014,844).

Ethanol has been used as a cosolvent. However, previous teachings (see, e.g., EP 0 616525) have taught away from using concentrations of ethanol greater than 5% for solution aerosol formulations for ß-agonists.

Historically, ethanol concentrations greater than 5% have been used only for steroid-based formulations with hydrofluoroalkane propellants.

The ß-agonist drug, formoterol ("eformoterol" in Europe) and its derivatives, have proven difficult to formulate in conventional aerosols. Such formulations have exhibited short shelf-lives and require refrigeration. Refrigeration is undesirable because many patients are required to carry the aerosol canisters on their persons. There remains, therefore, an important need for aerosol formulations for ß-agonist drugs such as formoterol and its derivatives that remain chemically and physically stable during storage at ambient conditions of temperature and humidity.

SUMMARY OF THE INVENTION

An objective of the present invention is to provide a pressurized metered dose inhaler that contains a stable formulation of a ß-agonist drug, which does not require the use of refrigeration.

Another objective of the present invention is to provide a stable formulation of a ß-agonist drug that is suitable for use as an aerosol, which does not require the use of refrigeration.

The above objectives and other objectives are surprisingly achieved by the following. The present invention provides a novel pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol formulation formulated from a composition comprising:

a ß-agonist drug;

at least one fluoroalkane propellant; and

greater than 5% by weight, based on total weight of the aerosol formulation, of a solvent that is capable of solubilizing or dissolving the ß-agonist drug.

The invention further provides a novel pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol formulation formulated from a composition comprising:

particles of a ß-agonist drug;

at least one fluoroalkane propellant; and

a surfactant that is capable of forming a suspension of the particles of ß-agonist drug.

The invention also provides a novel aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

a ß-agonist drug;

at least one fluoroalkane propellant; and

greater than 5% by weight, based on total weight of the aerosol formulation, of a solvent that is capable of solubilizing or dissolving the ß-agonist drug.

The invention further provides a novel aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

particles of a ß-agonist drug;

at least one fluoroalkane propellant; and

a surfactant that is capable of forming a suspension of the particles of ß-agonist drug.

The aerosol formulations are surprisingly stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates a chromatogram of formoterol fumarate formulated as a suspension; and

Fig. 2 illustrates a chromatogram of the formoterol fumarate after storage for 28 days at 40°C and 75% relative humidity.

DETAILED DESCRIPTION OF THE INVENTION

It has been unexpectedly discovered that the stability of aerosol formulations of solutions of a ß-agonist drug can be significantly improved by utilizing more than 5% by weight of a solvent capable of solubilizing or dissolving the ß-agonist drug. The ß-agonist drug can be any form that is suitable for application to the lungs or nasal passages of a human, such as base form or weak acid form. The present invention will be described with reference to the ß-agonist drug formoterol. The term "formoterol" is hereinafter understood to mean the base form of formoterol as well as the weak acid form of formoterol, unless stated otherwise. A preferred weak acid form of formoterol is formoterol fumarate.

The amount of ß-agonist drug utilized in the aerosol formulation will depend on the type of drug selected. For formoterol fumarate, the concentration utilized is usually about 1% by weight or less, preferably about 0.01% to about 0.02% by weight, based on the total weight of the aerosol formulation.

Any solvent that is suitable for inhalation and capable of solubilizing or dissolving the selected ß-agonist drug can be used. Examples of suitable solvents include alcohols, ethers, hydrocarbons, and perfluorocarbons. Preferably the solvent is short chain polar alcohols. More preferably, the

solvent is an aliphatic alcohol having from one to six carbon atoms, such as ethanol and isopropanol. The most preferred solvent is ethanol. Examples of suitable hydrocarbons include n-butane, isobutane, pentane, neopentane and isopentanes. Examples of suitable ethers include dimethyl ether and diethyl ether. Examples of suitable perfluorocarbons include perfluoropropane, perfluorobutane, perfluorocyclobutane, and perfluoropentane.

The solvent is usually present in an amount of from about 6 % to about 30% by weight, based on the total weight of the aerosol formulation. Preferably, the solvent is present in an amount of about 10 % to about 15% by weight. Based on the disclosure provided herein, one skilled in the art will recognize that lower concentrations of medicament usually require lower concentrations of solvent, and vice versa, in order to form a stable solution.

Any fluoroalkane propellant that is suitable for inhalation can be used. Examples of suitable fluoroalkanes include HFA-134a, HFA-227ea, HFA-125 (pentafluoroethane), HFA-152a (1,1-difluoroethane), and HFA-32 (difluoromethane). Hydrocarbon and/or aliphatic gases may be added to modify propellant characteristics as required. Preferably, the aerosol formulation is substantially free of chlorofluorocarbons. However, if desired chlorofluorocarbons can be utilized.

The propellant for solution formulations is usually present in an amount of from about 70% to about 94% by weight, based on the total weight of the aerosol formulation. A preferred aerosol formulation comprises HFA-134a in an amount less than about 90% by weight, ethanol in an amount greater than about 10% by weight, and formoterol fumarate in an amount of about 0.01% by weight. A particularly preferred aerosol formulation comprises about 85 % by weight of HFA-134a, about 15 % by weight of ethanol, and about 0.01 % by weight of formoterol fumarate.

Pressurized metered dose inhalers are now well known in the art.

Any pressurized metered dose inhaler that is suitable for application of drugs to the lungs or nose of a patient can be used. Pressurized metered dose inhalers usually are equipped with a metering valve having a spray orifice diameter of about 460μm. However, with the higher concentrations of solvent employed in the present invention, it may be desirable that the solvent evaporates as soon as possible after inhalation. This can be achieved by reducing the spray orifice diameter, for example, to 250μm, in combination with using solvent concentrations of about 10 to about 15% by weight. Based on the disclosure provided herein, one skilled in the art will be able to adjust the component composition to deliver a desired dose for the selected metered valve, without undue experimentation. For example, the composition may be altered to adjust the vapor pressure of the formulation. The aerosol formulation and metering valve are usually selected to provide a therapeutically effective amount of the ß-agonist drug per activation. An example of a therapeutically effective amount of formoterol fumarate is about 12 μg per activation.

It has also been unexpectedly discovered that stable aerosol formulations of suspensions of particles of a ß-agonist drug can be formed by utilizing the ß-agonist drug in combination with a surfactant that is capable of forming a suspension of the ß-agonist drug particles. The present invention will be described with reference to the ß-agonist drug formoterol.

The propellant can be any of the propellants described herein with reference to solution aerosol formulations. However, the propellant in suspension aerosol formulations can be utilized in amounts up to about 99.9% by weight, based on the total weight of the aerosol formulation.

The amount of ß-agonist drug utilized in the aerosol formulation will depend on the type of drug selected. For formoterol fumarate, the concentration utilized is usually about 1% by weight or less, preferably about 0.01% to about 0.02% by weight, based on the total weight of the aerosol

formulation.

The particle size of the ß-agonist drug should be suitable for inhalation into the nose or lung. Suitable average particle sizes are about 100µm and less, preferably about 20µm and less, and more preferably in the range of about 1 to about 10µm.

Any surfactant that is suitable for application to the lungs of a patient and which is capable of forming a suspension of particles of the ß-agonist drug can be utilized. Examples of suitable surfactants include polyalcohols such as polyethylene glycol (PEG 300), diethylene glycol monoethyl ether (Transcutol), polyoxyethylene(20) sorbitan monolaurate (Tween 20) or monooleate (Tween 80), propoxylated polyethylene glycol (Antarox 31R1), polyoxyethylene 4-lauryl ether (Brij 30), and surfactants having similar HLBs. Preferably, the surfactant is polyoxyethylene 4-lauryl ether (Brij 30). The surfactant is usually present in an amount of about 1% by weight or less.

A preferred suspension formulation comprises HFA-134a in an amount greater than 99% by weight, Brij 30 surfactant in an amount of about 0.002% by weight or greater, and formoterol fumarate in an amount of about 1% or less. A particularly preferred suspension formulation comprises about 99 % by weight of HFA-134a, about 0.02 % by weight of Brij 30, and about 0.02% by weight of formoterol fumarate. A particularly preferred formulation in a 19 ml canister comprises about 12.6 g/canister of HFA-134a, about 0.002 g/canister Brij 30, and about 0.002 g/canister of formoterol fumarate.

The following examples are presented merely to illustrate particular embodiments of the invention and not to limit the claims which are supported by the entire specification.

Examples I-3

Three suspension aerosols according the present invention were

formulated by combining the components shown in Table 1, using the following steps:

1. Weighing the solvent or surfactant into a plastic coated glass bottle or an aluminum canister.

2. Adding the weighed drug.

3. Crimping a valve upon the bottle or canister.

4. Adding a known amount of propellant through the valve into the bottle or canister.

5. Sonicating the formulation for about 5 minutes.

A Presspart, 19 mL, aluminum metered dose inhaler canister with a Bespak BK357, 63 μL metered valve was used, unless otherwise stated.

The properties of the Example aerosol formulations were tested using one or more of the following:

appearance (no external signs of leaking or deformation should be present);

leakage to meet United States Pharmacopeia 23 and National Formulary 18 standards;

canister contents to be within 10% of the mean;

drug per container to be within 25% of the mean;

chemical assay to be within 90.0-110% of label claim;

weight per metered dose;

unit spray content and content uniformity to meet Pharmacopeial Forum, vol. 22, no. 6 standards; and

aerodynamic size distribution and water determination.

The test results are shown in Table 1. By comparing the percent deposition in Stage 2, it was determined that formulations containing Brij 30 and Tween 20 were superior to those containing PEG 300. In addition, the data demonstrated that the Tween 20 formulation deposited a greater amount of drug on the actuator. Therefore, in order to minimize deposition

on this type of actuator, Brij 30 was a more useful surfactant in these formulations than was Tween 20.

Examples 4-7

Four solution aerosols according to present invention were formulated by combining the components shown in Table 2, using the method described in Example 1. To determine the stability of the solution aerosol formulations, Examples 6 and 7 were maintained for 1 month (28 days) at 40°C and 75% relative humidity, which are considered herein as accelerated conditions. The solution aerosol formulations were equilibrated at room temperature overnight before testing. The properties of the solution aerosol formulations were measured as in Example 1 and the results are shown in Table 2.

The data indicates that the dose delivered (by unit spray determination) after storage under accelerated conditions was lower than that obtained with the initial samples due to drug adsorption onto the valve gasket material. However, the solution aerosol formulations showed no signs of chemical deterioration.

Examples 8 and 9

Two solution aerosols according to present invention were formulated by combining the components shown in Table 3, using the method described in Example 1. To determine the stability of the solution aerosol formulations, Example 9 was maintained for 1 month (28 days) at 40°C and 75% relative humidity, which are considered herein as accelerated conditions. The solution aerosol formulations were equilibrated at room temperature overnight before testing. The properties of the solution aerosol formulations were measured as in Example 1 and the results are shown in Table 3.

The drug could not be recovered from the gasket materials during this study, which resulted in a loss of about 15% by weight. However, the

solution aerosol formulations showed no signs of chemical deterioration.

Examples 10-13

Four suspension aerosols according to present invention were formulated by combining the components shown in Table 4, using the method described in Example 1. To determine the stability of the suspension aerosol formulations, Examples 12 and 13 were maintained for 1 month (28 days) at 40°C and 75% relative humidity, which are considered herein as accelerated conditions. The suspension aerosol formulations were equilibrated at room temperature overnight before testing. The properties of the suspension aerosol formulations were measured as in Example 1 and the results are shown in Table 4.

After 28 days storage, the dose delivered (by unit spray determination) in Examples 12 and 13 was less than that obtained with the initial Examples 10 and 11, but not reduced by the same degree as with the solution formulation examples.

Examples 14-17

Four suspension aerosols according to present invention were formulated by combining the components shown in Table 5, using the method described in Example 1. To determine the stability of the suspension aerosol formulations, Examples 16 and 17 were maintained for 1 month (28 days) at 40°C and 75% relative humidity, which are considered herein as accelerated conditions. The suspension aerosol formulations were equilibrated at room temperature overnight before testing. The properties of the suspension aerosol formulations were measured as in Example 1 and the results are shown in Table 5.

The test data demonstrates that there was about a 10% loss of drug after storage under accelerated conditions in Examples 16 and 17, relative

to the initial Examples 14 and 15. This value is within acceptable limits and was in the area of 100% material balance (canister contents - drug per canister). In addition, the USP accepted method for determining particle size (Andersen impacter) was employed. The results showed that there was no chemical (as appearance of a known degradation product or loss of parent compound) or physical instability after storage including (1) as an increase in particle size (MMAD - mass median aerodynamic diameter), (2) change in the distribution (GSD - geometric standard deviation), (3) change in fine particle dose, or (4) change in fine particle fraction.

Examples 18 and 19

Two suspension aerosols according to present invention were formulated by combining the components shown in Table 6, using the method described in Example 1. The properties of the suspension aerosol formulations were measured as in Example 1 and the results are shown in Table 6.

Example 20

A suspension aerosol formulation was formed by combining 99.96 % by weight of HFA-134a, 0.02 % by weight formoterol fumarate, and 0.02 % by weight of Brij 30, using the method described in Example 1. HPLC chromatograms of the suspension aerosol, before and after storage for 28 days at 40°C and 75% relative humidity, were obtained as Figs. 1 and 2 respectively. In each Figure, only a single peak, representing the intact drug, was observed. No peaks representing breakdown products of the drug (expected to be at about 13 minutes) were found. Thus, the formoterol suspension aerosol exhibited long term stability.

Table1

Test		Example 1	Example 2	Example 3
Unit Spray Content	Drug per Dose (mcg)	8.27	8.53	5.97
	Shot Weight (mg)	82.15	81.10	80.70
Single Stage Liquid Impinger	Valve/Actuator (mcg)	26.59	40.73	11.27
	Throat/Neck (mcg)	25.00	16.36	13.59
	Stage 1 (mcg)	7.94	7.99	4.96
	Stage 2 (mcg)	40.87	39.92	27.71
	Material Balance (%)	66.50	73.50	41.60
	% in Stage 2	40.71	38.02	48.17
	Shot Weight (mg)	80.80	78.90	77.90
Formulation	HFA-134a	8.55550	8.71860	8.53550
	Surfactant	0.0017 (B3)	0.0017 (T2)	0.0018 (P3)
	Formoterol fumarate	0.00080	0.00079	0.00076

B3 - Brij® 30

T2 - Tween® 20

P3 - Polyethylene glycol 300

Test		Initial Data		28 Day Data	
		Example 4	Example 5	Example 6	Example 7
Unit Spray Content	Drug per Dose (mcg)	5.21	4.81	4.37	4.26
	Material Balance (%)	90	84	78	72
	Shot Weight (mg)	72.05	70.35	72.58	71.38
	Shot Number	7-10	7-10	6-9	11-14
Shot Weight	Shot Weight (mg)	70.0	71.3	74.9	73.1
	Shot Number	21-25	10-14	20-24	35-39
Single Stage Liquid Impinger	Valve/Actuator (mcg)	6.14	0.00	0.00	0.00
	Throat/Neck (mcg)	38.63	36.67	27.96	46.47
	Stage 1 (mcg)	4.00	3.69	2.44	0.00
	Stage 2 (mcg)	56.54	54.99	38.81	37.37
	Material Balance (%)	91	80	58	70
	% in Stage 2	53.69	57.67	56.08	44.57
	Shot Weight (mg)	72.10	72.96	76.39	72.60
	Shot Number	68-87	64-83	60-79	15-34
Unit Spray Content	Drug per Dose (mcg)	5.90	5.53	4.58	4.33
	Material Balance (%)	102	93	77	72
	Shot Weight (mg)	72.05	72.48	76.52	73.10
	Shot Number	54-57	54-57	51-54	51-57
Shot Weight	Shot Weight (mg)	71.1	72.3	77.0	73.8
	Shot Number	58-62	54-58	55-59	55-59
Moisture Content	Moisture (ppm)	442.08	624.41	-	-
Unit Spray Content	Drug per Dose (mcg)	6.24	6.13	5.42	4.79
	Material Balance (%)	107	104	92	79
	Shot Weight (mg)	72.28	72.42	75.80	73.52
	Shot Number	113-116	109-112	101-102	101-104
Shot Weight	Shot Weight (mg)	71.5	72.9	76.0	72.4
	Shot Number	122-126	118-122	108-112	110-114
Formulation	HFA-134a	16.912	17.064	17.224	16.753
	Ethanol	3.0062	3.0581	2.9963	3.0267
	Formoterol fumarate	0.00160	0.00164	0.00157	0.00163

Table 3

Test		Initial Data	28 Day Data
		Example 8	Example 9
Canister Contents	Drug per Canister (mg)	1.597	1.324
	% Recovery	100	85
Formulation	HFA-134a	16.993	16.853
	Ethanol	3.0336	3.0269
	Formoterol fumarate	0.00159	0.00156

Test		Initial Data		28 Day Data	
		Example 10	Example 11	Example 12	Example 13
Unit Spray Content	Drug per Dose (mcg)	14.45	14.22	13.32	11.10
	Material Balance (%)	92	89	85	77
	Shot Weight (mg)	80.0	82.9	80.75	80.75
	Shot Number	6-7	6-7	6-7	6-7
Shot Weight	Shot Weight (mg)	76.5	79.4	80.9	81.9
	Shot Number	8-12	8-12	18-22	8-12
Single Stage Liquid Impinger	Valve/Actuator (mcg)	32.72	31.36	23.36	27.90
	Throat/Neck (mcg)	31.21	27.93	19.11	17.47
	Stage 1 (mcg)	6.20	5.40	3.95	5.60
	Stage 2 (mcg)	75.95	76.92	78.58	69.57
	Material Balance (%)	94	90	78	83
	% in Stage 2	51.99	54.32	62.86	57.72
	Shot Weight (mg)	79.1	81.7	82.1	ND
	Shot Number	13-22	13-22	8-17	18-27
Unit Spray Content	Drug per Dose (mcg)	15.03	15.49	13.72	13.42
	Material Balance (%)	96	99	87	92
	Shot Weight (mg)	79.7	81.4	81.4	81.2
	Shot Number	50-51	50-51	50-51	43-44
Shot Weight	Shot Weight (mg)	78.9	81.8	80.9	79.7
	Shot Number	52-56	52-56	52-56	52-56
Moisture Content	Moisture (ppm)	428.91	342.21	-	-
Unit Spray Content	Drug per Dose (mcg)	13.58	12.67	10.55	14.73
	Material Balance (%)	87	81	72	116
	Shot Weight (mg)	79.4	ND	75.55	70.6
	Shot Number	86-87	82-83	91-92	91-92
Shot Weight	Shot Weight (mg)	69.3	80.5	79.7	73.0
	Shot Number	93-97	89-93	93-97	93-97
Formulation	HFA-134a	9.885	10.121	10.022	10.825
	Brij 30	0.00250	0.00227	0.00165	0.00152
	Formoterol fumarate	0.00194	0.00195	0.00195	0.00194

Table 5

Test		Initial Data		28 Day Data	
		Example 14	Example 15	Example 16	Example 17
Canister Contents	Drug per Canister (mg)	2.239	-	2.068	-
	% Recovery	118	-	108	-
Andersen Impactor	Valve (mcg)	-	9.86	-	15.25
	Actuator/Adapter (mcg)	-	19.35	-	9.37
	Induction Port/Cone (mcg)	-	20.37	-	17.15
	Stage 0 (mcg)	-	4.87	-	2.60
	Stage 1 (mcg)	-	3.31	-	2.15
	Stage 2 (mcg)	-	3.42	-	2.94
	Stage 3 (mcg)	-	11.64	-	13.67
	Stage 4 (mcg)	-	31.37	-	27.20
	Stage 5 (mcg)	-	20.43	-	19.80
	Stage 6 (mcg)	-	4.88	-	3.82
	Stage 7 (mcg)	-	1.25	-	0.75
	Stage F (mcg)	-	0.51	-	0.00
	Total S0-S7 (mcg)	-	81.17	-	72.93
	Total Drug Recovered (mcg)	-	131.26	-	114.70
	Material Balance (%)	-	90	-	75
	MMAD	-	2.5	-	2.5
	GSD	-	1.9	-	1.7
	Fine Particle Dose (mcg)	-	73.50	-	68.18
	Fine Particle Fraction (%)	-	73	-	75
Formulation	HFA-134a	9.899	10.642	10.134	10.219
	Brij 30	0.00163	0.00221	0.00188	0.00241
	Formoterol fumarate	0.00189	0.00189	0.00192	0.00192

Table 6

Test		Example 18	Example 19
Unit Spray Content	Drug per Dose (mcg)	10.87	9.55
	Material Balance (%)	89.0	78.5
	Shot Weight (mg)	78.6	78.0
	Shot Number	6-7	71-72
Unit Spray Content	Drug per Dose (mcg)	10.51	12.90
	Material Balance (%)	86.0	104.8
	Shot Weight (mg)	78.7	78.9
	Shot Number	8-9	73-74
Andersen Impactor	Valve (mcg)	5.93	9.14
	Actuator/Adapter (mcg)	28.91	29.02
	Induction Port/Cone (mcg)	30.03	20.18
	Stage 0 (mcg)	1.33	0.96
	Stage 1 (mcg)	1.64	1.32
	Stage 2 (mcg)	2.28	1.72
	Stage 3 (mcg)	9.54	8.45
	Stage 4 (mcg)	29.37	27.25
	Stage 5 (mcg)	27.71	27.52
	Stage 6 (mcg)	3.27	3.38
	Stage 7 (mcg)	0.00	0.00
	Stage F (mcg)	0.68	0.00
	Total S0-S7 (mcg)	75.14	70.60
	Total Drug Recovered (mcg)	140.69	128.93
	Material Balance (%)	107.7	103.8
	MMAD	2.3	2.5
	GSD	1.6	1.5
	Fine Particle Dose (mcg)	73	68
	Fine Particle Fraction (%)	69	75

Andersen Impactor	Valve (mcg)	5.64	-
	Actuator/Adapter (mcg)	28.58	-
	Induction Port/Cone (mcg)	23.56	-
	Stage 0 (mcg)	1.13	-
	Stage 1 (mcg)	1.56	-
	Stage 2 (mcg)	1.97	-
	Stage 3 (mcg)	9.95	-
	Stage 4 (mcg)	30.04	-
	Stage 5 (mcg)	27.51	-
	Stage 6 (mcg)	3.05	-
	Stage 7 (mcg)	0.00	-
	Stage F (mcg)	0.00	-
	Total S0-S7 (mcg)	75.21	-
	Total Drug Recovered (mcg)	132.98	-
	Material Balance (%)	103.3	-
	MMAD	2.5	-
	GSD[a]	1.5	-
	Fine Particle Dose (mcg)	73	-
	Fine Particle Fraction (%)	74	-
Formulation	HFA-134a	12.8169	12.6705
	Brij 30	0.00230	0.00220
	Formoterol fumarate	0.002044	0.001970

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to those of ordinary skill in the art that various changes and modifications can be made to the claimed invention without departing from the spirit and scope thereof.

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Claims:

1. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol formulation formulated from a composition comprising:

a ß-agonist drug;

at least one fluoroalkane propellant; and

greater than 5% by weight, based on total weight of said aerosol formulation, of a solvent that is capable of solubilizing or dissolving said ß-agonist drug.

2. A pressurized metered dose inhaler according to claim 1, wherein said metering valve is constructed and arranged to provide metered doses of said ß-agonist drug in an amount that is thereapuetically effective.

3. A pressurized metered dose inhaler according to claim 1, wherein said metering valve is constructed and arranged to provide metered doses of said ß-agonist drug in an amount of about 12 μg per actuation of said meterering valve.

4. A pressurized metered dose inhaler according to claim 1, wherein said fluoroalkane comprises 1,1,1,2-tetrafluoroethane.

5. A pressurized metered dose inhaler according to claim 1, wherein said formulation is substantially free of chlorofluorocarbons.

6. A pressurized metered dose inhaler according to claim 1, wherein said propellant is present in an amount of from about 70 to about 94%

by weight.

7. A pressurized metered dose inhaler according to claim 1, wherein said solvent is present in an amount of at least 10% by weight.

8. A pressurized metered dose inhaler according to claim 1, wherein said solvent is present in an amount of at least 15% by weight.

9. A pressurized metered dose inhaler according to claim 1, wherein said solvent is present in an amount in the range of from greater than 5% to about 30% by weight, based on the total weight of said aerosol formulation.

10. A pressurized metered dose inhaler according to claim 1, wherein said solvent is selected from the group consisting of ethers and alcohols.

11. A pressurized metered dose inhaler according to claim 1, wherein said solvent comprises an aliphatic alcohol having from 1 to about 6 carbon atoms.

12. A pressurized metered dose inhaler according to claim 1, wherein said solvent comprises ethanol.

13. A pressurized metered dose inhaler according to claim 1, wherein said solvent is more polar than said propellant.

14. A pressurized metered dose inhaler according to claim 1, wherein said ß-agonist drug comprises formoterol.

15. A pressurized metered dose inhaler according to claim 14, wherein said formoterol is present in an amount of about 1% by weight or less, based on the total weight of said aerosol formulation.

16. A pressurized metered dose inhaler according to claim 14, wherein said formoterol is present in an amount of about 0.01 to about 0.02% by weight, based on the total weight of said aerosol formulation.

17. A pressurized metered dose inhaler according to claim 14, wherein said formoterol comprises formoterol fumarate.

18. A pressurized metered dose inhaler according to claim1, wherein said aerosol formulation is substantially free of a surfactant.

19. A pressurized metered dose inhaler according to claim 14, wherein said formoterol comprises formoterol fumarate in an amount of up to about 1 % by weight, said solvent comprises ethanol in an amount of greater than 5% to about 30% by weight, and said propellant is present in an amount of from about 70% to about 94% by weight, all weights based on the total weight of said aerosol formulation.

20. A pressurized metered dose inhaler according to claim 1, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

21. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol

formulation formulated from a composition comprising:

particles of a ß-agonist drug;

at least one fluoroalkane propellant; and

a surfactant that is capable of forming a suspension of said particles of ß-agonist drug.

22. A pressurized metered dose inhaler according to claim 21, wherein said metering valve is constructed and arranged to provide metered doses of said ß-agonist drug in an amount that is therapeutically effective.

23. A pressurized metered dose inhaler according to claim 21, wherein said metering valve is constructed and arranged to provide metered doses of said ß-agonist drug in an amount of about 12 μg per actuation of said metering valve.

24. A pressurized metered dose inhaler according to claim 21, wherein said fluoroalkane comprises 1,1,1,2-tetrafluoroethane.

25. A pressurized metered dose inhaler according to claim 21, wherein said formulation is substantially free of chlorofluorocarbons.

26. A pressurized metered dose inhaler according to claim 21, wherein said propellant is present in an amount up to about 99.9% by weight.

27. A pressurized metered dose inhaler according to claim 21, wherein said ß-agonist drug comprises formoterol.

28. A pressurized metered dose inhaler according to claim 27, wherein

said formoterol has an average particle size of less than about 100 μm.

29. A pressurized metered dose inhaler according to claim 27, wherein said formoterol has an average particle size of less than about 20 μm.

30. A pressurized metered dose inhaler according to claim 27, wherein said formoterol has an average particle size of from about 1 μm to about 10 μm.

31. A pressurized metered dose inhaler according to claim 21, wherein said aerosol formulation is substantially free of a solvent.

32. A pressurized metered dose inhaler according to claim 27, wherein said formoterol is present in an amount of about 1% by weight or less, based on the total weight of said aerosol formulation.

33. A pressurized metered dose inhaler according to claim 27, wherein said formoterol is present in an amount of about 0.01 to about 0.02% by weight, based on the total weight of said aerosol formulation.

34. A pressurized metered dose inhaler according to claim 27, wherein said formoterol comprises formoterol fumarate.

35. A pressurized metered dose inhaler according to claim 21, wherein said surfactant is present in an of at least about 0.002 % by weight, based on the total weight of said aerosol composition.

36. A pressurized metered dose inhaler according to claim 21, wherein

said surfactant is present in an of about 1 % by weight or less, based on the total weight of said aerosol composition.

37. A pressurized metered dose inhaler according to claim 21, wherein said surfactant is at least one selected from the group consisting of polyalcohols.

38. A pressurized metered dose inhaler according to claim 21, wherein said surfactant comprises at least one selected from the group consisting of polyethylene glycol, diethylene glycol monoethyl ether, polyoxyethylene(20) sorbital monolaurate or monooleate; and polyoxyethylene 4-lauryl ether.

39. A pressurized metered dose inhaler according to claim 21, wherein said surfactant comprises polyoxyethylene 4-lauryl ether.

40. A pressurized metered dose inhaler according to claim 27, wherein said formoterol comprises formoterol fumarate in an amount of up to about 1 % by weight, said surfactant comprises polyoxyethylene 4-lauryl ether in an amount of about 1% by weight or less, and said propellant is present in an amount 99.9% by weight, all weights based on the total weight of said aerosol formulation.

41. A pressurized metered dose inhaler according to claim 21, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

42. An aerosol formulation adapted for use in a pressurized aerosol

container, said aerosol formulation being formulated from a composition comprising:

a ß-agonist drug;

at least one fluoroalkane propellant; and

greater than 5% by weight, based on total weight of said aerosol formulation, of a solvent that is capable of solubilizing or dissolving said ß-agonist drug.

43. An aerosol formulation according to claim 42, wherein said fluoroalkane comprises 1,1,1,2-tetrafluoroethane.

44. An aerosol formulation according to claim 42, wherein said formulation is substantially free of chlorofluorocarbons.

45. An aerosol formulation according to claim 42, wherein said propellant is present in an amount of from about 70 to about 94% by weight.

46. An aerosol formulation according to claim 42, wherein said solvent is present in an amount of at least 10% by weight.

47. An aerosol formulation according to claim 42, wherein said solvent is present in an amount of at least 15% by weight.

48. An aerosol formulation according to claim 42, wherein said solvent is present in an amount in the range of from greater than 5% to about 30% by weight, based on the total weight of said aerosol formulation.

49. An aerosol formulation according to claim 42, wherein said solvent is selected from the group consisting of ethers and alcohols.

50. An aerosol formulation according to claim 42, wherein said solvent comprises an aliphatic alcohol having from 1 to about 6 carbon atoms.

51. An aerosol formulation according to claim 42, wherein said solvent comprises ethanol.

52. An aerosol formulation according to claim 42, wherein said solvent is more polar than said propellant.

53. An aerosol formulation according to claim 42, wherein said ß-agonist drug comprises formoterol.

54. An aerosol formulation according to claim 53, wherein said formoterol is present in an amount of about 1% by weight or less, based on the total weight of said aerosol formulation.

55. An aerosol formulation according to claim 53, wherein said formoterol is present in an amount of about 0.01 to about 0.02% by weight, based on the total weight of said aerosol formulation.

56. An aerosol formulation according to claim 53, wherein said formoterol comprises formoterol fumarate.

57. An aerosol formulation according to claim 42, wherein said aerosol formulation is substantially free of a surfactant.

58. An aerosol formulation according to claim 53, wherein said formoterol comprises formoterol fumarate in an amount of up to about 1 % by

weight, said solvent comprises ethanol in an amount of greater than 5% to about 30% by weight, and said propellant is present in an amount of from about 70% to about 94% by weight, all weights based on the total weight of said aerosol formulation.

59. An aerosol formulation according to claim 42, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

60. An aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

particles of a ß-agonist drug;

at least one fluoroalkane propellant; and

a surfactant that is capable of forming a suspension of said particles of ß-agonist drug.

61. An aerosol formulation according to claim 60, wherein said fluoroalkane comprises 1,1,1,2-tetrafluoroethane.

62. An aerosol formulation according to claim 60, wherein said formulation is substantially free of chlorofluorocarbons.

63. An aerosol formulation according to claim 60, wherein said propellant is present in an amount up to about 99.9% by weight.

64. An aerosol formulation according to claim 60, wherein said ß-agonist drug comprises formoterol.

65. An aerosol formulation according to claim 64, wherein said formoterol has an average particle size of less than about 100 μm.

66. An aerosol formulation according to claim 64, wherein said formoterol has an average particle size of less than about 20 μm.

67. An aerosol formulation according to claim 64, wherein said formoterol has an average particle size of from about 1 μm to about 10 μm.

68. An aerosol formulation according to claim 60, wherein said aerosol formulation is substantially free of a solvent.

69. An aerosol formulation according to claim 64, wherein said formoterol is present in an amount of about 1% by weight or less, based on the total weight of said aerosol formulation.

70. An aerosol formulation according to claim 64, wherein said formoterol is present in an amount of about 0.01 to about 0.02% by weight, based on the total weight of said aerosol formulation.

71. An aerosol formulation according to claim 64, wherein said formoterol comprises formoterol fumarate.

72. An aerosol formulation according to claim 60, wherein said surfactant is present in an of at least about 0.002 % by weight, based on the total weight of said aerosol composition.

73. An aerosol formulation according to claim 60, wherein said surfactant is present in an of about 1 % by weight or less, based on the total

weight of said aerosol composition.

74. An aerosol formulation according to claim 60, wherein said surfactant is at least one selected from the group consisting of polyalcohols.

75. An aerosol formulation according to claim 60, wherein said surfactant comprises at least one selected from the group consisting of polyethylene glycol, diethylene glycol monoethyl ether, polyoxyethylene(20) sorbital monolaurate or monooleate; and polyoxyethylene 4-lauryl ether.

76. An aerosol formulation according to claim 60, wherein said surfactant comprises polyoxyethylene 4-lauryl ether.

77. An aerosol formulation according to claim 64, wherein said formoterol comprises formoterol fumarate in an amount of up to about 1 % by weight, said surfactant comprises polyoxyethylene 4-lauryl ether in an amount of about 1% by weight or less, and said propellant is present in an amount 99.9% by weight, all weights based on the total weight of said aerosol formulation.

78. An aerosol formulation according to claim 60, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

Fig. 1

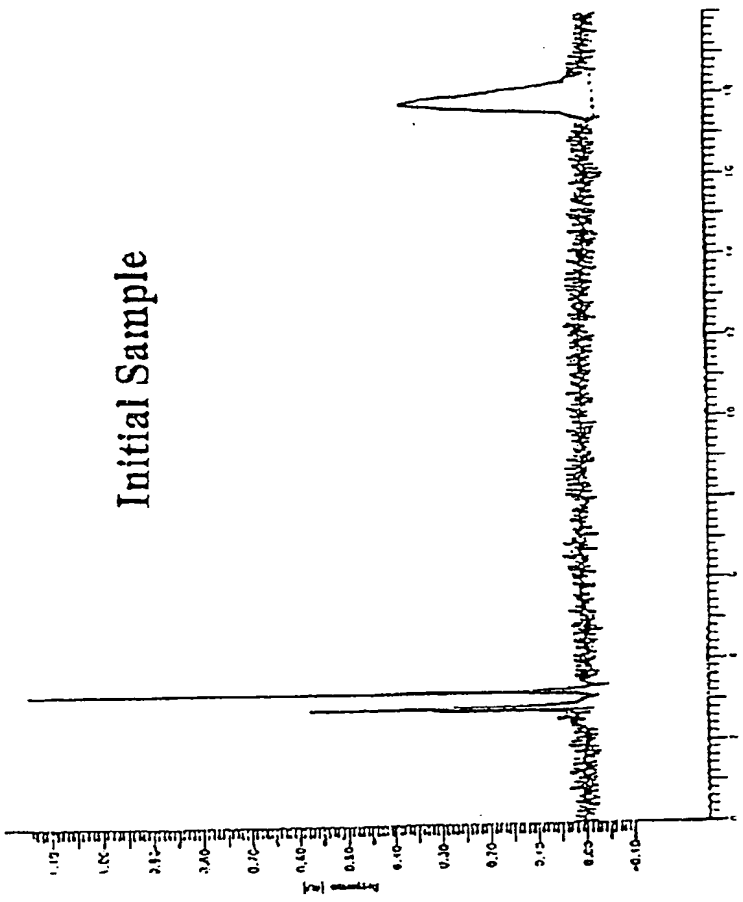

Fig. 2